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Triple therapy with first generation HCV protease inhibitors: Lead-in or no lead-in phase?

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Summary

The standard therapeutic approach currently recommended for patients infected with genotype 1 hepatitis C virus (HCV) is the triple therapy combining pegylated interferon (PEG-IFN), ribavirin (RBV) and NS3/NS4 protease inhibitors, boceprevir or telaprevir [1]. Protease inhibitors (PIs) are direct acting antiviral drugs (DAA) which, when added to PEG-IFN and RBV, are able to achieve a significant gain in terms of sustained virological response (SVR), both in naïve and treatment-experienced patients [2–5]. The use of these new molecules, despite its incontestable benefits, reveals on the other hand new challenges: the emergence of variants with reduced sensitivity to PIs, the development of new or higher rate of side effects, drug to drug interactions, and significant increase in the overall cost of antiviral therapy. Among the two DAAs commonly used in combination with PEG-IFN and RBV (PEG-IFN/RBV) for the treatment of genotype 1 HCV patients, boceprevir has been licensed with a lead-in phase, while telaprevir has been licensed without. EMA approved regimens of both drugs are reported in Figs. 1 and 2. The lead-in phase represents an initial period of 4 weeks of dual therapy with PEG-IFN/RBV, in standard doses, followed by triple therapy. The concept of lead-in phase was initiated by the Schering–Plough company in order to improve efficacy of boceprevir-based triple therapy. Indeed, by lowering HCV RNA level, a short course of PEG-IFN/RBV may theoretically reduce the risk of viral breakthrough or resistance. However, there is still much controversy regarding the utility of the lead-in phase, some authors advocating its role in improving, and/or predicting triple therapy effectiveness, while others view it as a useless complication of the therapeutic regimen, its chief disadvantage being the inconvenience to the patient.

Lead-in phase and triple therapy effectiveness

The impact of lead-in phase on triple therapy effectiveness has been investigated in two therapeutic trials, one in treatment-naïve, and the other in treatment-experienced patients. In treatment-naïve patients, the effect of a lead-in phase of PEGIFN/RBV therapy is based on the phase II trial SPRINT-1 evaluating boceprevir-based triple therapy [6]. Though it was not the primary end point, the comparison between arms with or without lead-in phase showed no statistically significant difference in terms of SVR rates (66% *vs.* 60%, $p > 0.05$). In terms of virological breakthrough, there was a tendency of lower rate in patients treated with lead-in (4 *vs.* 9%, $p = 0.06$). In contrast, the rate of rapid virological response at week 4 of triple therapy was significantly higher in patients treated with lead-in *vs.* no lead-in phase (62% *vs.* 38%, $p < 0.001$). According to the response-guided therapy (RGT) regimen (Fig. 1), this result suggests that lead-in phase might increase the number of patients eligible for a short treatment duration with boceprevir based-triple therapy (28 weeks) [2]. There are no available data regarding lead-in phase in naïve patients receiving telaprevir-based triple therapy. In treatment-experienced patients, the impact of lead-in phase on triple therapy effectiveness is based on the phase III REALIZE study evaluating telaprevir [4]. There was no difference in terms of SVR rates between patients treated with or without a lead-in phase, neither for previous relapsers (88% *vs.* 83%), nor partial responders (54% *vs.* 59%) nor null responders (33% *vs.* 29%). Neither was virological breakthrough rate significantly influenced by lead-in phase (1 *vs.* 1% in previous relapser and 17 *vs.* 19% in previous non-responders). In prior relapsers, however, the rate of rapid virological response at week 4 of triple therapy was significantly higher with lead-in *vs.* no lead-in phase (89 *vs.* 70%, $p < 0.05$). Because telaprevir was licensed with RGT in non-cirrhotic relapser patients (Fig. 2), this result suggests that lead-in may increase the percentage of patients eligible for shorter duration treatment. In summary, there is no clear advantage of lead-in in terms of SVR rates in patients treated with boceprevir or telaprevir-based triple therapy. However, in patients eligible for RGT, lead-in may shorten the duration of treatment in a significant number of cases by increasing the RVR rate on triple therapy (Table 1). By contrast, in patients eligible for fixed duration of treatment, lead-in could be avoided, including patients receiving boceprevir-based triple therapy (Table 1).

Lead-in phase as predictor: impact on therapeutic decision

In the setting of new challenges raised by the use of PIs – such as development of viral resistance associated with treatment failure,

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Abbreviations: HCV, hepatitis C virus; RVR, rapid virological response; SVR, sustained viral response; RBV, ribavirin; IFN, interferon; PEG-IFN, pegylated interferon; DAA, direct acting antivirals; PIs, protease inhibitors; RGT, response-guided therapy; IL28B, interleukin 28B.

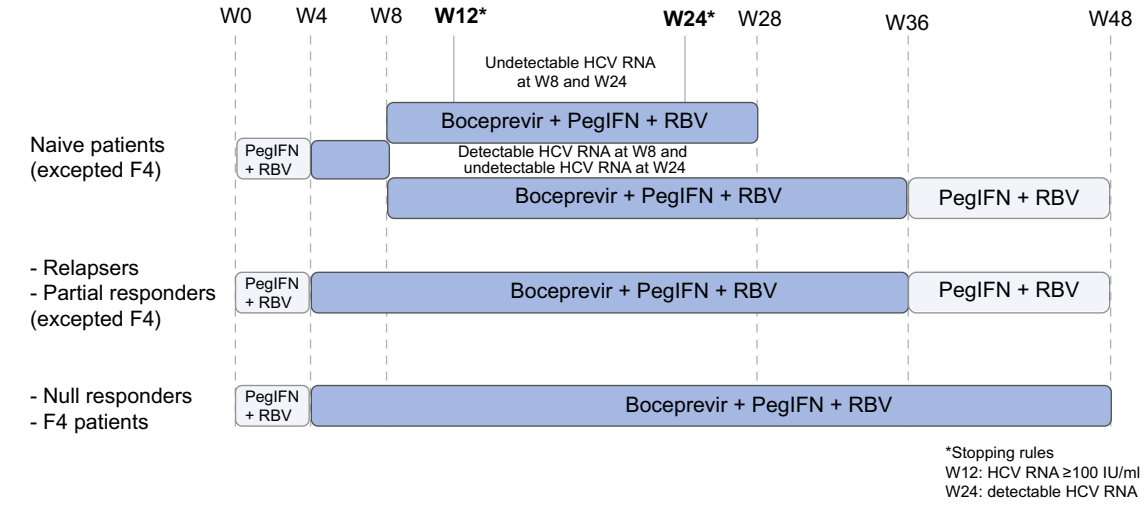

Fig. 1. EMA approved regimen of boceprevir-based triple therapy.

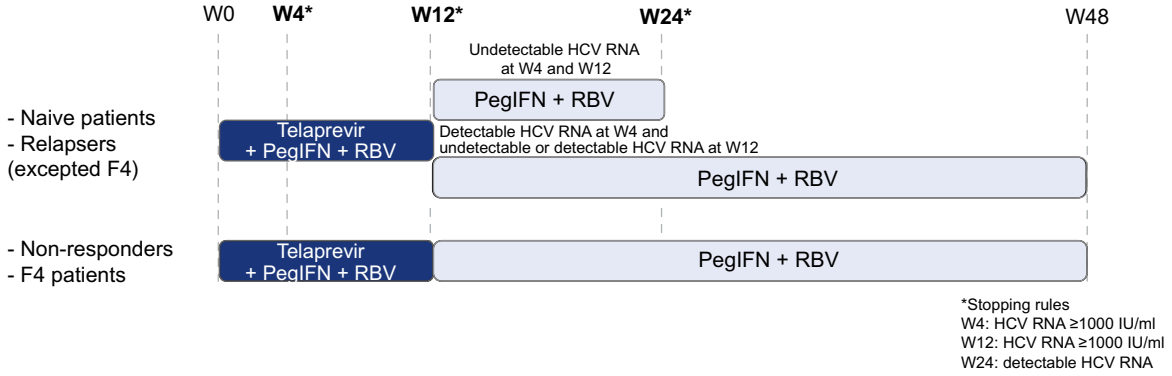

Fig. 2. EMA approved regimen of telaprevir-based triple therapy.

side effects or treatment cost – predictors of response to triple therapy are highly needed. Phase 3 trials have suggested that lead-in phase, by assessing the sensitivity to interferon, is able to predict triple therapy effectiveness [2,4,5,7]. *Post hoc* analysis of boceprevir phase III trials showed that viral load decline >1.0 log (interferon sensitive response) or <1.0 log (poor interferon response) at the end of lead-in was the strongest independent predictor of SVR, in both naïve and treatment experienced patients [8]. Viral load decline was also predictive of resistant variants emergence (41% in patients with <1.0 log decline *vs.* 6% in patients with >1.0 log of decrease) [2,5]. However, the main issue to address is whether viral load decline during lead-in phase is enough accurate for the prediction of SVR and to have an impact on the therapeutic decision. In naïve patients, the relationship between viral load decline during lead-in phase and response to triple therapy has been investigated in the SPRINT-2 study evaluating boceprevir [2]. Viral load decline at the end of lead-in phase was related to the SVR rate, since a less than 1.0 log viral load decline (poor interferon response) was associated with a 28% SVR rate in RGT arm and 40% in fixed-duration arm, while a more than 2.0 log viral load decline was associated with an SVR rate >80%. However, given its low negative predictive value, lead-in may have no major impact on the decision of initiating or not triple therapy in poor interferon responders. The only decision impact could be the choice of fixed duration treatment that achieves a higher rate of SVR compared to RGT, in this subgroup of patients [2]. On the other hand, lead-in phase may avoid the disadvantages of triple therapy in highly-interferon sensitive patients with rapid virological response (RVR), i.e., HCV RNA undetectable at week 4 of lead-in. Indeed, in this subgroup of patients, PEG-IFN/RBV was able to achieve an SVR rate higher than 90%, similar to the SVR rates achieved with boceprevir- or telaprevir-based triple therapy [2,3]. Therefore, despite the lack of a randomized study, PEG-IFN/RBV could be a therapeutic alternative to triple therapy in genotype 1 RVR patients. There are some concerns about the duration of treatment that is 48 weeks compared to 24 weeks with triple therapy. Only the subgroup of RVR patients with low baseline viral load may benefit from a 24-week course of PEG-IFN/RBV [9]. Another concern is the rather small proportion of patients with RVR, less than 10%, requiring a large number of patients to be screened. Interleukin-28-B (*IL28B*) genotyping could be one way to select patients for PEG-IFN/RBV, as more than 30% of the patients with CC genotype may achieve an RVR [10]. Accordingly, French guidelines have proposed a 4-week course of PEG-IFN/RBV prior to triple therapy (boceprevir or telaprevir-based) in naïve patients with *IL-28B* CC genotype and fibrosis score ⩽F2 [11] (Table 1). In a recent pub-

Table 1. Usefulness of lead-in phase in boceprevir- or telaprevir-based regimen according to patients status, naïve or treatment-experienced.

	Boceprevir-based triple therapy	Telaprevir-based triple therapy
Naïve patients		
Lead-in Y/N	Yes	Yes
Target population	Non-cirrhotic	*IL28B* CC and F ≤2 patients (± low viral load at baseline)
Impact	Higher proportion of patients eligible for short duration treatment Selection of patients eligible for RGT *vs.* fixed duration treatment Selection of patients eligible for dual therapy (*IL28B* CC and F ≤2 ± low viral load at baseline)	Selection of patients eligible for dual therapy
Relapsers		
Lead-in Y/N	No	Yes
Target population	-	Non-cirrhotic
Impact	-	Higher proportion of patients eligible for short duration treatment
Partial responders		
Lead-in Y/N	No	No
Null responders		
Lead-in Y/N	?	Yes
Target population	-	All
Impact	-	Re-evaluation of triple therapy in poor interferon responders

lished study, this strategy was considered as cost-effective, at least in the setting of boceprevir-based triple therapy [12]. On the other hand, a retrospective study from phase II telaprevir trials has suggested that CC patients may benefit from shortening triple therapy to 12 weeks instead of the usual 24 weeks [13]. This should be confirmed by larger prospective studies. In treatment-experienced patients, the accuracy of lead-in for the prediction of SVR to triple therapy has been investigated in RESPOND-2 and PROVIDE studies evaluating boceprevir, and in the REALIZE study evaluating telaprevir [4,5,7]. In prior relapsers or partial responders, SVR rates according to viral load decline <1.0 log *vs.* >1.0 log at the end of lead-in were respectively 37% *vs.* 81% and 37% *vs.* 61% in the boceprevir RESPOND-2 study and, 62% *vs.* 88% and 56% *vs.* 59% in the telaprevir REALIZE study [4,5]. Therefore, SVR rates were rather high, even in poor interferon responders, suggesting that lead-in may have no major impact on treatment decision, i.e., initiating or not triple therapy, in prior relapsers or partial responders. In prior null responders, SVR rates according to viral load decline <1.0 log *vs.* >1.0 log at the end of lead-in were respectively 36% *vs.* 55% in the boceprevir PROVIDE study and 15% *vs.* 54% in the telaprevir REALIZE study [4,7]. In the REALIZE study, the relatively low SVR rate in poor interferon responders, i.e., 15%, may question the use of telaprevir in this very difficult-to-treat population. It should be noted that about half of the patients had severe fibrosis, a baseline parameter also highly predictive of SVR in prior null responders. Indeed, the SVR rate was lower that 10% in case of extensive fibrosis associated with poor interferon response. In the boceprevir PROVIDE study, the higher SVR rate in poor interferon responders, i.e., 36%, could be explained by the small proportion of patients with severe fibrosis. Moreover, the small sample size population could hamper the interpretation of the results. In summary, lead-in phase is a good predictor of SVR to triple therapy in treatment experienced patients but may have no major impact on therapeutic decision, except in prior null responders (Table 1). In this subgroup of patients, lead-in seems to have some advantages, at least for the decision of initiating telaprevir-based triple therapy, and the benefit-risk ratio should be re-evaluated in case of poor interferon response. In patients with undetermined previous response profile, lead-in phase might be informative for reclassification, but finally without any significant impact on therapeutic decision.

Lead-in phase and tolerance with triple therapy

By testing the tolerance to PEG-IFN/RBV prior to initiating triple therapy, lead-in phase could be helpful for the management of patients, especially in cirrhotics. The French CUPIC study reported a high risk of serious adverse events, including death, in this population when exposed to triple therapy [14]. The lead-in phase may permit dosage adjustment of PEG-IFN and RBV according to clinical tolerance, especially hematological toxicity, as well as the initiation, if needed, of growth factors, prior to introducing triple therapy. In a randomized trial evaluating the management of anemia in boceprevir-treated patients, RBV dosage adjustments as first line during lead-in phase had no major impact on

SVR rate, compared to EPO use [15]. These results should be tempered by the fact that less than 10% of the patients had cirrhosis, and by the notable decrease of SVR rate in patients with severe fibrosis randomized in the RBV arm. Specific studies are needed in cirrhotic patients prior to draw definitive conclusions. Moreover, we do not know whether PEG-IFN/RBV dosage adjustment during lead-in phase has a different impact on SVR compared to dosage adjustment during triple therapy.

Lead-in phase, practical issues and cost-effectiveness

There are important practical issues that argue against the use of the lead-in phase, as the increase in the total duration of treatment (minimal duration of 28 weeks in naïve patients), the inconvenience to the patient, who is subjected to an initial period of 4 weeks of PEG-IFN/RBV therapy requiring an additional visit and blood sample test at the end of lead-in. Thus, the lead-in phase may complicate the therapeutic scheme, both for the patient and for the physician. Another important practical issue is the short delay required for HCV RNA results at the end of lead-in phase, in case of treatment decision. Along with practical issues of therapy also comes an increased overall treatment cost, which, when added to the cost of antiviral therapy using PIs, may result in a less favorable cost/benefit profile. Until now, the lead-in strategy was validated as cost-effective regarding the selection for dual therapy of naïve genotype 1 patients with fibrosis score F2 in the setting of boceprevir-based triple therapy [12]. Indeed, selective treatment strategy guided by RVR in naïve patients was cost-effective compared to universal boceprevir-response guided therapy. In the setting of telaprevir-based triple therapy, selective treatment strategy guided by the *IL-28B* genotype was also cost-effective but the lead-in strategy was not evaluated. The authors recommend using PI-free strategies as first-line therapy in patients with *IL28B* CC genotype or in those who achieve RVR. Cost-effectiveness analysis of selective treatment strategies in prior null responders needs further consideration.

Conclusions

In conclusion, lead-in phase with PEG-IFN/RBV offers no clearly proven virological benefit, except a shorter duration of treatment in non-cirrhotic naïve patients receiving boceprevir-based regimen or in relapsers receiving telaprevir-based regimen. In view of its value for the prediction of triple therapy effectiveness, lead-in phase should be considered in two subgroups of patients: (1) those who could benefit from a 24-week course of PEG-IFN/RBV, i.e., low viral load at baseline, with CC *IL-28B* genotype and mild liver disease $\leqslant$F2, (2) those who are poor interferon responders, especially prior null responders in whom initiation of triple therapy should be re-evaluated. An additional benefit would be the possibility of tailoring PEG-IFN/RBV dosage during the lead-in phase in patients with poor tolerance, but this strategy needs additional investigations, especially in cirrhotics. For all the other categories of patients, there is no clear evidence that justifies the use of lead-in phase. In the approaching era of more efficient therapeutic regimens in chronic hepatitis C, it is probable that the terms of this controversy will be no longer relevant.

Conflict of interest

Alina Pascal: no conflict of interest. Lawrence Serfaty: consulting, advisory committees or review panels (Axcan Pharma, BMS, Gilead, GSK, Janssen, MSD, Pfizer, Roche, Schering Plough, Tibotec, Vertex), grant/research support (Roche; Schering–Plough), speaking and teaching (Axcan Pharma, BMS, Gilead, Janssen, MSD, Roche, Schering Plough, Vertex).

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